claims of this application or of the cited copending applications.[1]

III. The Section 112, Paragraph 1, Rejection

In the May 1st Office Action, the Examiner rejected applicants' Claims 186, 187, 199-208, and 217-220 under 35 USC §112, ¶1. This is the second rejection under this section of the statute that has been made by the Examiner against this application.

The first rejection was made in the Office Action dated April 19, 2005. In that Office Action, the Examiner alleged that the "present invention is unpredictable unless experimentation is shown for the other capsaicin receptor antagonists beside the ones disclosed in claims 187 and 208" and concluded that the "level of experimentation needed to determine various capsaicin receptor antagonists would be able to treat pain is undue." (4/19/05 Office Action at page 5.)

In an amendment filed on July 19, 2005, applicants responded to this rejection based on the factors for determining undue experimentation set forth in In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), specifically, factor 2 (the amount of direction or guidance provided) and factor 5 (the state of the prior art).

With regard to factor 2, applicants pointed out that their specification disclosed a capsaicin receptor binding assay in Example 10 and an assay for capsaicin receptor antagonism in Example 11. As to factor 5, applicants submitted an excerpt from the

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[1] In making the double patenting rejections, the Examiner stated that the method claimed in Claims 201-207 and 217-222 of this application comprises "administering to [a] mammal a therapeutic dose of a capsaicin receptor antagonist that is not a capsaicin analogue" and that the copending applications are concerned with a "method for treating pain with the administering of a therapeutically effective amount of a capsaicin receptor broadly." To clarify the record, applicants note that certain of their claims directed to the treatment of neuropathic pain do not require an antagonist that is not a capsaicin analogue and that the cited co-pending applications are concerned with capsaicin receptor modulators rather than capsaicin receptors per se. Along these same lines, in connection with the §112, ¶1, rejection (see Section III), the Examiner referred to the "diaryl piperazine compounds of the formula disclosed in claims 187 and 208." Although the formula used in those claims does encompass diaryl piperazine compounds, it is not limited to such compounds.

1995 edition of the text Burger's Medicinal Chemistry and Drug Discovery which showed that high throughput screening was well known in the art and widely practiced long before applicants' earliest priority date. Based on these showings, applicants argued that the Wands factors were satisfied since identifying capsaicin receptor antagonists would not require undue experimentation in view of the assays taught by applicants and the state of the art.

In the next Office Action dated October 19, 2005, the Examiner withdrew the §112, paragraph 1, rejection in view of applicants' submission. In the current Office Action, the Examiner has entered a new §112, paragraph 1, rejection. In this case, the Examiner asserts:

> The working examples are limited to the administration of diaryl piperazine compounds of the formula disclosed in claims 187 and 208.
>
> No working examples showing other capsaicin receptor antagonists other than capsaicin analogues were effective in treating pain. (5/1/06 Office Action at page 5.)

The Examiner then concludes that "undue experimentation would be required to practice the invention as it is claimed in its current scope" (5/1/06 Office Action at page 6).

Applicants believe that the same considerations which were applicable to the original §112, ¶1, rejection are applicable here, namely, (1) the amount of direction or guidance provided by applicants and (2) the state of the prior art.

Beginning with the amount of direction or guidance provided by applicants, Examples 18a through 18e of applicants' specification set forth well know procedures for testing drugs to determine if they are effective in treating pain. These examples are entitled: CFA Arthritis Model, Mechanical Allodynia, Cold Allodynia, Mechanical Hyperalgesia, and Thermal Hyperalgesia. They thus span a spectrum of pain types from chronic arthritic pain through various manifestations of neuropathic pain. These five

examples direct the reader to the following pain literature, copies of which are submitted herewith:[2]

Bennet and Xie, Pain 1988, 33:87-107.

Bertorelli R, et al., Br J. Pharmacol. 1999 128(6):1252-8.

Chaplan et al. J. Neurosci. Methods 1994, 53:55-63.

Hargreaves K, Dubner R, Brown F, Flores C, Joris J. Pain. 1988 32(1):77-88.

Koch et al. Analgesia 1996, 2(3), 157-164.

Stein C, Millan M J, Herz A. Pharmacol Biochem Behav. 1988 31(2):455-51.

Tal M, Eliav E. Pain. 1996 March; 64(3):511-8.

Also submitted herewith are copies of selections from the following textbooks, reference manuals, and review articles which discuss the process of testing compounds for their effectiveness in treating pain. All of these materials are dated prior to applicants' earliest priority date. Not surprisingly, applicants' specification cites to many of the same original articles as cited in these standard texts or to similar articles from the same groups of authors. Indeed, applicants believe that even without the references in their specification to specific pain study articles, a person skilled in the art could easily practice the present invention without undue experimentation by simply turning to one or more of these reference materials or other readily available standard works:

Handbook of Laboratory Animal Science, Chapter 12, "Animal Models in Pain Research," (P. Svendsen and J. Hau, editors), CRC Press, Boca Raton FL, 1994, pp. 137-144.

Textbook of Pain, Chapter 14, "Assessing Transient and Persistent Pain in Animals," (P. Wall and R. Melzack, editors), Churchill Livingstone, Edinburgh, Scotland, 1999, pp. 359-369.

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[2] A Supplemental Modified PTO 1449 Form listing the references referred to herein is also submitted herewith.

Current Protocols in Pharmacology, "Models of Pain: Hot-Plate and Formalin Test in Rodents," A. Bannon, John Wiley & Sons, Hoboken NJ, 1998, pp. 5.7.1-5.7.11.

Progress in Pain Research and Management, "A Practical Guide for the Use of Animal Models in the Study of Neuropathic Pain," (Boivie et al., editors), IASP Press, 1994, Seattle WA, pp. 295-338

The Pharmacology of Pain, "Animal Models of Analgesia," (A. Dickenson and J. Besson, editors), Springer-Verlag, 1997, Berlin, Germany, pp. 1-20.

Molecular Medicine Today, "Animal Models for Pain Research," Walker et al., Elsevier Science, New York NY, 1999, pp. 319-321.

As these materials demonstrate, the testing of compounds for their effectiveness in treating pain was well established as of applicants' priority date. Indeed, such testing was common place at pharmaceutical companies which market pain medicines. As just one example, attached hereto as Exhibit A is a table of experimental data that Pharmacia/G.D. Searle submitted to the FDA as part of their application for approval of the pain reliever Valdecoxib (Bextra®). The test results reported in this table were obtained using assays of the same type as set forth in the above textbooks/reference manuals and in applicants' Examples 18a-18e.[3]

In view of these considerations, applicants respectfully submit that the Examiner's §112, ¶1, rejection is unfounded. To a person skilled in the art, determining whether a compound is effective in relieving pain involves routine, not undue, experimentation.

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[3] As further support for the conventional nature of pain model testing, applicants direct the Examiner's attention to Reference 29 of applicants' June 7, 2004 PTO-1449 form in which animal pain models of the types discussed in the above reference materials were used to demonstrate the analgesic effectiveness of the capsaicin receptor agonist, SDZ 249-665.

IV. Conclusion

Based on the foregoing, applicants believe that this application is now in condition for allowance. Accordingly, reconsideration and the issuance of a notice of allowance for the application are respectfully requested.

Respectfully submitted,

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